IN THE SPECIFICATION

Please amend the paragraph beginning at page 2, line 13 with the following rewritten paragraph:

Tiotropium bromide is the preferred anticholinergic agent because of its high potency and long duration. However, tiotropium is difficult to formulate in dry powder form to provide acceptable performance in terms of dose efficacy using prior art DPIs. Dose efficacy depends to a great deal on delivering a stable and high fine particle dose (FPD) out of the dry powder inhaler. The FPD is the respirable dose mass out of the dry powder inhaler with an aerodynamic particle size below 5 μm. Thus, when inhaling a dose of dry medication powder it is important to obtain by mass a high fine particle fraction (FPF) of particles with an aerodynamic size preferably less than 5 μm in the inspiration air. The majority of larger particles (>5 μm) does not follow the stream of air into the many bifurcations of the airways, but get stuck in the throat and upper airways, where the medicament is not giving its intended effect, but may instead be harmful to the user. It is also important to keep the dosage to the user as exact as possible and to maintain a stable efficacy over time, and that the medicament dose does not deteriorate during normal storage. For instance, Boehringer Ingelheim KG (BI) markets tiotropium bromide under the proprietary name of ~~Spiriva®~~ SPIRIVA®. Surprisingly, in a recent investigation into the inhalability of ~~Spiriva®~~ SPIRIVA® we have found that the ~~Spiriva®~~ SPIRIVA®/~~Handihaler®~~ HANDIHALER® system from BI for administration by inhalation of doses contained in gelatin capsules shows poor performance and has short in-use stability.

Please amend the paragraph beginning at page 3, line 1 with the following rewritten paragraph:

Thus, there is a need for improvement regarding a medical product comprising inhalable dry powder doses of tiotropium bromide, for instance ~~Spiriva®~~ SPIRIVA®, and suitably adapted inhaler devices for the purpose of administration.

Please amend the paragraph beginning at page 3, line 19 with the following rewritten paragraph:

In another aspect of the invention a type of inhaler is disclosed, which may accept at least one sealed, moisture-tight, dry container of a dose of tiotropium, e.g. ~~Spiriva®~~ SPIRIVA®, and deliver said dose with a consistent FPD, over the expected shelf life of the product.

Please amend the paragraph beginning at page 4, line 19 with the following rewritten paragraph:

Tiotropium is a new important anticholinergic substance for treatment of asthma and COPD but tiotropium is known in the industry to have problems maintaining in-use stability due to sensitivity to moisture. This fact is also documented in the report 'COLLEGE TER BEOORDELING VAN GENEESMIDDELEN MEDICINES EVALUATION BOARD; PUBLIC ASSESSMENT REPORT; ~~Spiriva®~~ SPIRIVA® 18 µg, inhalation powder in hard capsules; RVG 26191' (2002-05-21) on page 6/28 under 'Product development and finished product' a very short in-use stability of the ~~Spiriva®~~ SPIRIVA® product (9 days) is reported and a brittleness of the capsule in the blister pack and a very low FPD: 'about 3 ug'.

Please amend the paragraph beginning at page 5, line 5 with the following rewritten paragraph:

In the light of the above information given in the quoted report a test program was set up for the physical stability of the ~~Spiriva®~~ SPIRIVA® product with respect to the compatibility of the formulation together with the components of the device according to Food and Drug Administration (FDA) 'Guidance for Industry; Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing, and Controls Documentation' page 37/62 'Drug product stability' lines 1209 - 1355. In 'Guidance for Industry; Stability Testing of Drug Substances and Drug Products; DRAFT GUIDANCE; B. Container/Closure' pages 35 and 36/110 lines 1127 – 1187, FDA states: 'Stability data should be developed for the drug product in each type of immediate container and closure proposed for marketing, promotion, or bulk storage. The possibility of interaction between the drug and the container and closure and the potential introduction of extractables into the drug product formulations during storage should be assessed during container/closure qualification studies using sensitive and quantitative procedures.' and further 'Loss of the active drug substance or critical excipients of the drug product by interaction with the container/closure components or components of the drug delivery device is generally evaluated as part of the stability protocol. This is usually accomplished by assaying those critical drug product components, as well as monitoring various critical parameters (e.g., pH, preservative, effectiveness). Excessive loss of a component or change in a parameter will result in the failure of the drug product to meet applicable specifications.'

Please amend the paragraph beginning at page 5, line 28 with the following rewritten paragraph:

According to FDA publication 'Guidance for Industry; Stability Testing of Drug Substances and Drug Products' a 3 week test program in accelerated conditions (40 ± 2 °/ 75 ± 5 RH) for the container closure of the ~~Spiriva®~~ SPIRIVA® product in this case the capsule and the blister pack and the impact of the capsule and the blister package on the FPD was set up and tested.

Please amend the paragraph beginning at page 6, line 3 with the following rewritten paragraph:

~~Spiriva®~~ SPIRIVA® powder formulation in bulk and ~~Spiriva®~~ SPIRIVA® capsules from our local pharmacy where introduced to the laboratory together with the ~~Handihaler®~~ HANDIHALER®. The laboratory was set up to perform in-vitro tests according to European Pharmacopoeia (EP) and US Pharmacopoeia (USP) using two Andersen cascade impactors. All analytical work where then performed according to standardized methods for Physical Tests and Determinations for Aerosols, metered-dose inhalers and dry powder inhalers described in pharmacopoeias (e.g. USP 2002 <601>) using a state of the art High Performance Liquid Chromatograph (HPLC) system.

Please amend the paragraph beginning at page 6, line 13 with the following rewritten paragraph:

~~Spiriva®~~ SPIRIVA® tests

Test S1

Aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using ~~Spiriva®~~ SPIRIVA® formulation from bulk powder loaded

into originator capsules during relative humidity below 10 %. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 6, line 22 with the following rewritten paragraph:

Aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using commercial ~~Spiriva®~~ SPIRIVA® capsules purchased from our local pharmacy. Test performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 6, line 28 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using commercial ~~Spiriva®~~ SPIRIVA® capsules purchased from our local pharmacy. From the blister holding 5 capsules one capsule was withdrawn and the remaining 4 capsules were put 4 days into 40 °C and 75 % Rh. The blister containing the 4 capsules was then put in an exicator for 2 h before tests were performed. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 7, line 6 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using commercial ~~Spiriva®~~ SPIRIVA® capsules

purchased from our local pharmacy. From the blister holding 5 capsules one capsule was withdrawn and the remaining 4 capsules were put 13 days into 40 °C and 75 % Rh. The blister containing the 4 capsules was then put in an exicator for 2 h before tests were performed. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 7, line 16 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using commercial ~~Spiriva®~~ SPIRIVA® capsules purchased from our local pharmacy. From the blister holding 5 capsules one capsule was withdrawn and the remaining 4 capsules were put 21 days into 40 °C and 75 % Rh. The blister containing the 4 capsules was then put in an exicator for 2 h before tests were performed. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 7, line 27 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using ~~Spiriva®~~ SPIRIVA® formulation from bulk powder loaded during relative humidity below 10 % into containers made to act as a high barrier seal, in this case aluminum foils from Alcan Singen Germany and then sealed to absolute tightness. The aluminum containers were put in an exicator for 2 h before the ~~Spiriva®~~ SPIRIVA® powder formulation was loaded from the aluminum containers into the originator capsules at a relative humidity below 10 %. The test was performed with 4 kPa

pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 8, line 8 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using ~~Spiriva®~~ SPIRIVA® formulation from bulk powder loaded during relative humidity below 10 % into containers made to act as a high barrier seal, in this case aluminum foils from Alcan Singen Germany and then sealed to absolute tightness. The sealed aluminum containers were put into climate chambers for 7 days at 40 °C and 75 % Rh. The aluminum containers were put in an exicator for 2 h before the ~~Spiriva®~~ SPIRIVA® powder formulation was loaded from the aluminum containers into the originator capsules at a relative humidity below 10 %. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 8, line 21 with the following rewritten paragraph:

An in-use stability test of the aerodynamic fine particle fraction of metered and delivered dose out of ~~Handihaler®~~ HANDIHALER® using ~~Spiriva®~~ SPIRIVA® formulation from bulk powder loaded during relative humidity below 10 % into containers made to act as a high barrier seal, in this case aluminum foils from Alcan Singen Germany and then sealed to absolute tightness. The sealed aluminum containers were put into climate chambers for 14 days at 40 °C and 75 % Rh. The aluminum containers were then put in an exicator for 2 h before the ~~Spiriva®~~ SPIRIVA® powder formulation was loaded from the aluminum containers

into the originator capsules at a relative humidity below 10 %. The test was performed with 4 kPa pressure drop over the ~~Handihaler®~~ HANDIHALER® at room temperature and laboratory ambient conditions.

Please amend the paragraph beginning at page 9, line 5 with the following rewritten paragraph:

A test was also made outside the stability test program to evaluate our proprietary inhaler, the so-called C-haler, in comparison with the ~~Handihaler®~~ HANDIHALER® using a tiotropium formulation. The C-haler cartridge used high barrier seals made out of aluminum foils from Alcan Singen Germany and the containers where filled volumetrically with 5 mg of the ~~Spiriva®~~ SPIRIVA® powder formulation in bulk. The test was performed using a 4 kPa pressure drop over the C-haler at room temperature and laboratory ambient conditions. The results from the Andersen impactor tests were calculated on fine particle fraction based on delivered dose as well as on metered dose and converted to FPD. The results are given in Table 1 below.

Please amend the paragraph beginning at page 9, line 17 with the following rewritten paragraph:

The results of tests S1-5 and HBS1-3 are plotted in Figure 1. The Y-axis is designated '% of commercial ~~Spiriva®~~ SPIRIVA® FPD'. This relates to the FPD out from the ~~Handihaler®~~ HANDIHALER®, where 100 % is the FPD from a fresh sample from the pharmacy.

Please amend the Table 1 beginning at page 9, line 22 with the following rewritten table:

Calculation based on	~~Spiriva®~~ SPIRIVA® in ~~Handihaler®~~ HANDIHALER®, commercial sample, FPD	~~Spiriva®~~ SPIRIVA® in C-haler, FPD
Metered dose	18 %	47 %
Delivered dose	36 %	56 %

Please amend the paragraph beginning at page 9, line 25 with the following rewritten paragraph:

Conclusion of the tests performed on ~~Spiriva®~~ SPIRIVA®

Surprisingly we have found and concluded in our tests that tiotropium is extremely sensitive to moisture and that a conventional packaging into gelatin capsules used for a majority of respiratory products will seriously affect the FPD. The results show that there is a need for a dry, moisture-tight high barrier seal enclosing the tiotropium formulation to preserve the original fine particle fraction. Not so surprisingly in the light of these findings, we have also found that the tiotropium formulation must be properly protected also during the in-use time if further reduction of the FPD shall be avoided. Eliminating the gelatin capsule has an unexpected, big, positive effect on the performance of the ~~Spiriva®~~ SPIRIVA® formulation.

Please amend the paragraph beginning at page 10, line 10 with the following rewritten paragraph:

The tests carried out show that the moisture content of the gelatin capsule reduces the FPD out of the ~~Handihaler®~~ HANDIHALER® with approximately 50 % from the time of loading the dose into a capsule until the point in time when the product reaches the market. Loading

~~Spiriva®~~ SPIRIVA® doses into dry containers made of materials presenting high barrier seal properties and then storing the loaded containers in 40 °C and 75 % Rh, before transferring the ~~Spiriva®~~ SPIRIVA® doses to originator capsules and performing the same tests using ~~Handihaler®~~ HANDIHALER® as before, no change can be detected in the fine particle dose (FPD), even after long periods of time. The FPD of ~~Spiriva®~~ SPIRIVA® in gelatin capsules, however, is further diminishing during the in-use time of the product and the FPD has been shown to drop up to another 20 % after 5 days of storage in 40 °C and 75 % Rh in an in-use stability test, due to the breaking of the moisture barrier in the opened blister secondary package. Table 1 shows that our propertiary C-haler using high barrier containers shows a 2.6 times higher performance than ~~Handihaler®~~ HANDIHALER® with respect to FPD based on metered dose.

Please amend the paragraph beginning at page 10, line 27 with the following rewritten paragraph:

Metered doses of the ~~Spiriva®~~ SPIRIVA® powder formulation are today at the originator manufacturing site loaded into gelatin capsules. A gelatin capsule contains typically 13-14 % water by weight in the dose forming stage and after the capsules have been loaded they are dried in a special process in order to minimize water content. A number of dried capsules are then put in a common blister package. Details about suitable state-of-the-art capsule materials and manufacturing processes may be studied in the German Patent Application DE 101 26 924 A1. The remaining small quantity of water in the capsule material after drying is thus enclosed in the blister package and some water will be released into the enclosed air, raising the relative humidity in the air. The equilibrium between the captured air inside the package and the gelatin capsule will generate a relative humidity inside the blister package that will negatively affect the FPD of tiotropium powder out of the dry powder inhaler.

Please amend the paragraph beginning at page 11, line 10 with the following rewritten paragraph:

It is interesting to note that the big majority of dry powder formulations of many kinds of medicaments are not seriously affected by enclosed moisture in the capsule material or by normal storage variations in the relative humidity of the surrounding air. Surprisingly, our investigation has shown tiotropium to be very much different. Tiotropium powder is very much affected by very small amounts of water such that it tends to stick to wall surfaces and to agglomerate. By some mechanisms the FPD becomes less over time. Since the capsules are only used as convenient, mechanical carriers of ~~Spiriva®~~ SPIRIVA® doses, a solution to the moisture problem would be not to use capsules at all, but rather to directly load doses into containers made of dry packaging material with high barrier seal properties during dry ambient conditions, preferably below 10% Rh.

Please amend the paragraph beginning at page 14, line 2 with the following rewritten paragraph:

An inhaler providing a prolonged delivery of a dose during the course of a single inhalation constitutes a preferred embodiment of an inhaler for the delivery of the tiotropium powder formulation, e.g. ~~Spiriva®~~ SPIRIVA®. An Air-razor method as described in our publication US 2003/0192539 A1 is preferably applied in the inhaler to efficiently and gradually aerosolize the dose when delivered to the user. Surprisingly enough, applying an inhaler for a prolonged delivery and using the Air-razor method on a dose comprising tiotropium in ~~Spiriva®~~ SPIRIVA® formulation results in a FPD at least twice as big as that from the state-of-the-art ~~Handihaler®~~ HANDIHALER®.